DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service, Center for Biologics Evaluation & Research
U.S. Food & Drug Administration

Laboratory of Molecular and Developmental Immunology,
Division of Monoclonal Antibodies, HFM-561
Building 29B, Room 3NN10, 1401 Rockville Pike, Bethesda, MD 20852

BLA 97-1251 Product Review - SIMULECT (basiliximab) - Novartis Pharma AG

Date: 8 May 1998

From: Frederick W. Miller, BLA Product Reviewer and Chair, Laboratory of Molecular and Developmental Immunology, DMA, CBER, N29B, 2G11, HFM-561, Bethesda, MD 20892, 301-827-0659, millerf@cber.fda.gov

To: BLA 97-1251 (**FILE**)

Subject: BLA 97-1251 Product Review
Date of BLA submission: 12-NOV-97
Date received by FDA: 12-NOV-97
Application filing letter: 17-DEC-97
Priority Decision date: 12-MAY-98

Through: Kathryn E. Stein, Director DMA, CBER

cc: David Essayan, DCTDA
Carol Trapnell, DCTDA
Lauren Black, DCTDA
Janice Brown, DEL
Pat Hasemann, DIS
Terry Neeman, DBE
Earl Dye, DARP

Recommendation: ***After a complete and thorough review of BLA 97-1251 -- based upon evaluation of IND 6050, the pre-BLA filing materials, a 93 volume paper and electronic (eBLA) submission, and additional information submitted by the sponsor as supplements dated March 25, April 7, April April 17, May 1, and May 6, 1998 -- I recommend approval of this product for human use under the conditions specified in the SIMULECT package insert.***

Therapeutic:	**SIMULECT (basiliximab, SDZ CHI 621) - Recombinant chimeric (murine/human) monoclonal antibody (IgG1K) anti-IL-2Ra (CD25).**
Manufacturer:	**Novartis Pharmaceuticals AG Lichtstrasse 35 4002, Basel, Switzerland**
Sponsor contact:	**John Cutt, Novartis; Phone: 973-503-5012**
Manufacturer Contact:	Dr. Urs Giger, Basel Switzerland; Phone: 0041-61-324-3821 last inspection May 1996, file number FCSZ019
Indication:	Prophylaxis of organ rejection in *de novo* renal transplantation

My initial review of BLA 97-1251 was based upon evaluation of IND 6050, pre-BLA filing materials, and a 93 paper volume BLA and electronic (eBLA) submission.

My final review includes evaluation of additional information submitted by the sponsor as multiple supplements listed above in response to our queries. The following is a summary of my complete review which contains, in some sections, verbatim portions of the BLA submission.

Table of Contents

1. Characterization of the new drug substance, basiliximab (SDZ CHI 621)

1.1 Physico-chemical characterization

The new drug substance, basiliximab, and the drug product, Simulect Lyophilisate for Injection, are manufactured by Novartis Pharma AG, Basel, Switzerland. Simulect Lyophilisate for Injection is a lyophilized powder (20 mg/vial), to be reconstituted for administration. Basiliximab, or SDZ CHI 621, is a chimeric mouse/human monoclonal antibody which reacts specifically with the alpha chain of the IL-2 receptor, the CD25 antigen, expressed on the surface of T-cells. The antibody functions as an immunosuppressant and is for use in renal transplantation to reduce the incidence of organ rejection. The new drug substance, basiliximab (SDZ CHI 621), has been extensively characterized; see section 1.2 (of Section 3 of the BLA, pages 3-1 and following [3-1 ff]) for the physicochemical, bioanalytical, and biological characterization. Details of the characterization are provided in section 2.1.2 (of section 3 of the BLA, 3-1 ff).

Basiliximab is a chimeric (mouse/human) monoclonal antibody of the IgG k class and is comprised of two light and two heavy chains; the variable antigen binding regions are derived from a murine antibody (the RFT5 cell antibody), and the constant regions are of human origin (see Fig. 1. 2-25)

13 lines

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12 PAGES

4.2.7 ——— , through ——— system

——— through

4.2.8 Dispensing of bulk solution

4 lines

4.3 Definitions of lots and batches

A harvest lot is defined as the amount of harvest collected during a period of time

6 lines

4.4 Reviewer Comments - Purification and down-stream processing

The purification process appears to be a logical, relatively simple and straightforward design allowing efficient purification of the product. In process controls appear appropriate to assess for contaminants and by-products during purification and to reproducibly produce a pure product. ——— ***holding container extractables are mentioned as being*** — ***but are not defined or quantitated in this submission.***

5. Process Validation

5.1 Validation for genetic work

The details of the genetic validation of the cell banks (MCB, WCB, and ECB) are presented in Section 2.3.3.1 and 2.3.3.2 (of Section 3 of the BLA), following the

information on construction of the production cell line and the establishment of the ——— respectively. Regarding cell bank media: ——— ——— used during production of the MCB was of ——— and certified to be free of mycoplasma and viruses. The MCB itself was tested and found to be free of viral contaminants of

2 lines

The cell banks were analyzed to check the fidelity of the coding sequences and to provide evidence for genetic stability. DNA fingerprint profiles were generated for the

6 lines

Sequencing of the coding regions of both light and heavy chains was carried out by

14 lines

Genetic stability testing was performed on cells from extended cell banks (ECBs) leading to material made in the pilot facility and this was compared to ECBs created by the final commercial process. Data from these comparisons showed by ———

5.2 Validation of the new process in building ———

Drug substance batches

3 lines

3 lines

12 lines

One problem arose during operation – when microbial contamination occurred from leakage of valves in the medium transfer line caused by broken membranes and a leaky rotor seal on the bioreactor (——— ; after fixing this problem 1 subsequent operation has resulted in sterile cultures.

A contamination of the harv st collection tank —— and harvest storage tank —— due to problems in a transfer line, caused contamination of —lots of production run for ————————). Although modifications were made in the transfer line and more frequent sterility testing will be performed, no further data from later lots confirming that these changes will reduce contamination is presented! Drug substance batch —— was purified to assess the role the contamination might have induced in the final product, but it will not be used for human use; no evidence of increased levels of degradation products in the intermediates nor any elevation of endotoxin levels were observed.

A contamination of batch —— also occurred in the ———————— step from incomplete sanitation of tank —— where the WFI was stored for dilution of the harvest; this tank is now sanitized with an improved procedure, but the subsequent batch —— also showed contamination of the ———————— step because of high bioburden in the production lots per above (3-393).

5.3 Life-time / limit of use of columns

No limits for time of use or number of runs have been set for: ———————— since in the — runs performed to date the expansion heights have been ———— during the loading and ———— after compression; ————, since no changes have been seen

in the 3 lines

5.4 Reviewer Comments - Process Validation

A number of bioburden problems arose during the processing of last several drug substance batches related to broken membranes in transfer lines, leaking rotor seals in the bioreactor, and incomplete sanitation of holding tanks. Although endotoxin was low in all these batches, and the bioburden levels may not have impacted the potency and purity of the final product, additional evidence should be provided of correction of these problems by confirming low bioburdens in the recent batches after the many in process changes have been made to correct these bioburden problems.

A limit on all column use/life-times should be defined based upon deterioriation of column performance as assessed by ——— model column testing program.

6. Adventitious agent testing

An extended test program for detection of adventitious agents in cells from the MCB, WCB, ECB and bulk harvests was conducted at ———
——— These results are shown in Table 5, Table 6, Table 7 and Table 8 (3-289 ff).

6.1 MCB testing

The MCB was found to be negative for:

- bacteria = 10% of the vials tested sterile

- mycoplasma by ——— ;

6 lines

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1 page

6.3 WCB testing

Adventitious agents testing for the WCB included:

7 lines

6.4 ECB testing

Adventitious agents testing performed on ECB (production run for batch —— =

8 lines

6.5 Transmissible spongiform encephalopathy (TSE) issues

SIMULECT has been stated to comply with the CPMP guidance and does not contain any ingredients (active substance or excipient) derived from animal sources and will comply with Commission Directive 97/534/EC when it takes effect. Ingredients derived from animal or human sources have been used in the manufacturing of basiliximab (2.4.2.4, 3-421):

6 lines

Precautions taken re TSEs include:

- No animal materials have been or will be sourced from countries with high incidence of TSE;
- Tissues are designated as risk category IV (no detectable infectivity) for ——, which was certified as suitable for human use;

- [redacted] 4 lines
- [redacted]
- During purification at least ' steps greatly decrease the load of any contaminating infectious agent by 12-18 logs.

6.6 Reviewer Comments - Adventitious agent testing

The data provided show that the cell banks are free from contamination by mycoplasma, bacteria, fungi and yeast. Tests for [redacted] *viruses on the MCB were negative; these tests were done only on the MCB, which was prepared using* [redacted] *As expected, the* [redacted]

[redacted] 11 lines

7. Validation for cell growth, harvesting, and antibody purification

7.1 Overview

The process has been transferred from the

[redacted] 12 lines

The quality of antibody product

harvested at different time points during continuous cultivation remains high despite any variability in process parameters.

Cell cultivation is carried out under [redacted] Determination of total microbial counts on the bulk harvest and at various steps during purification shows that the [redacted]

The removal of process-related contaminants has been investigated for the direct cited production batches. Step 4 in the antibody purification uses a [redacted] column, and the column material itself can leach and subsequently contaminate the product. [redacted] was determined using [redacted] Samples of the eluate from Step 4 showed a low level ([redacted] of [redacted] leaching. Samples tested after Steps 5 and 6 of the purification showed that after the [redacted] purification (Step 6) the amount of [redacted] detectable had been reduced to below [redacted] i.e., less than the quantifiable limit. The results for removal of [redacted] are consistent with data from pilot scale studies. Removal of host cell proteins (HCP) was similarly investigated, using a sensitive [redacted] test. Samples after Step 3 ([redacted] filtration) showed the presence of substantial amounts of HCP (values above [redacted]). Purification on the [redacted] column removed most of the contaminating HCP (circa a [redacted] reduction) and the [redacted] chromatography resulted in a further reduction; the final values were below [redacted] and are lower than those seen at pilot scale. DNA was determined by [redacted] at several steps in the purification process. The [redacted] column (Step 4) and the [redacted] column (Step 5) were the main steps for DNA removal; following the latter step, and reflected in the final product, the values for DNA were [redacted], the detection limit for the assay. This corresponds to [redacted] of DNA per [redacted] vial of drug product. The levels of the culture medium ingredients [redacted], and [redacted] were shown to be reduced to low levels (i.e., levels of [redacted] basiliximab) by factors of [redacted] respectively after the [redacted] chromatography step; the level of [redacted] is probably further reduced after the [redacted] step since it would be expected to be washed out of the [redacted] column.

Low levels of multimeric variants of the antibody are found during all steps of the purification. These variants, which are mainly dimers, amount to less than 1 % of the drug substance and are shown to be further reduced at Step 6 so that levels in the final product are almost negligible. The purification process did not appreciably alter the isoform distribution of basiliximab, and as shown by batch analyses (see Table 9, 2-48) the levels of all impurities were consistently low (i.e., less than [redacted] total impurities and degradants) in the validation of the commercial process.

7.2 *Reviewer Comments - Validation for cell growth, harvesting, and antibody purification*

These processes appears appropriate and drug production in the new facility under the new conditions appears to result in a product that has acceptable levels of process related contaminants.

8. Validation for virus clearance and removal

8.1 Overview

Potential contamination of the drug substance (and hence drug product) with viruses is a major issue in the production of antibodies derived from mammalian cell cultivation. Because viruses could be present either as endogenous viruses in the cell line, or as adventitious contaminants, the clearance of viruses during the purification process was therefore validated in an exact scale-down of the production process. The studies were conducted at _____, and the validation was carried out according to both the FDA Points to Consider document and the CPMP Guidance on Viral Validation Studies.

It is known that murine hybridoma cell lines secrete an endogenous virus and that this is also the case for the cell line developed for the production of basiliximab. This was taken into account in selecting the model viruses for the validation of clearance. — virus types were selected for study:

15 lines

A validation study at the pilot scale purification process had shown that —. and — are not cleared at the — step, and that no clearance of — can be expected at the — step. Thus, these particular tests were not repeated in the production-scale validation. The — step was not tested as it had not been found effective in pilot scale validation. A summary of the viral reduction data is found in Table 10, 2-49.

The details of the study on inactivation and clearance of potential viral contaminants can be found in section 2.4.2.3 (of Section 3 of the BLA). A statement regarding measures taken to avoid potential TSE contamination has been included at the end of the Process Validation section (see 2.4.2.4 of Section 3 of the BLA).

8.2 Reviewer Comments - Validation for virus clearance and removal

The results show that the purification process is efficient in removal of the — model viruses. For the endogenous — virus there is a high and reproducible clearance of virus with — steps tested contributing to the overall result. The number of virus-like particles determined in the bulk harvest is typically — . Assuming a worst-case scenario with — virus particles per liter of bulk harvest culture and a volume of — culture broth required to produce one dose of the drug product — then the — reduction established in this investigation confers a safety margin of — The other — model viruses are also removed effectively, with each process step contributing to viral clearance. The validation results indicate that an endogenous murine virus and a representative selection of potential adventitious viruses are effectively cleared.

9. Standards, drug substance specifications and analytical methods

9.1 Reference Standard

The reference standard for the new drug substance basiliximab (SDZ CHI 621) is lot — , material that was produced in the pilot plant, which has been used for the characterization studies reported. The new drug substance specifications, and results for lot — , are shown Tables 3 and 4 of section 2.6.2.1 (of Section 3 of the BLA). Careful documentation of: — — all support the use of lot — as an appropriate reference standard. *No SOPS are presented for qualifying a new reference standard.*

9.2 Drug Substance Specifications

Quality characteristics	*Requirements*
Physical properties	
Appearance	
Color	
pH	
Identity	
Purity	
By- and degradation products	
By- and degradation products under reducing conditions	
Assay	
Biological activity	
SEC	
Bacterial endotoxins	
Count of organisms	
Heavy metals	

9.3 Batch analysis comparisons

Assessments of batches ——— show good consistency in levels of by-products, organisms, endotoxin, heavy metals, DNA, protein A, ——— and host cell proteins (Tables 3-4, 3-434 ff)

9.4 Analytical Methods

The analytical methods and their validations are provided as Appendices (of Section 3 of the BLA) . See Appendix G for the analytical methods for analysis of the drug substance, basiliximab. The bioanalytical test methods and their validation are provided as Appendix B. The routine analytical test methods (and validations) for ingredients and reagents are provided as Appendix A.

9.5 Reviewer Comments - Standards, Drug substance specifications and analytical methods

The reference standard, drug substance specifications and limits and analytic methods all appear appropriate and should result in the consistent production of equivalent batches of drug substance. ***Validation of the ——— assay by the ——— assay has not been provided and no SOPS are presented for qualifying a new reference standard.***

10. Drug Substance Stability - Container/Closure System

10.1 Overview

Bulk basiliximab, new drug substance made at commercial scale is stored at ——— ——— ——— ——— The bottles are ——— ——— Acceptance testing includes cleanliness, tightness of closure and extractables according to USP but **details for extractables are not provided.** During early development bulk new drug substance was stored in glass bottles at 2-8 degrees C., while a stability study was conducted on ——— ———). No significant decrease in biological activity could be demonstrated at any of the temperatures examined. Evidence of degradation was clear at ——— ; degradant formation was also noted at the ——— ——— and — indicated that basiliximab was stable at ——— ——— , but — indicated that accumulation of aggregates was greater at ——— ——— . Based

on this preliminary data, the storage temperature for bulk new drug substance was therefore changed to below [redacted] A comparison of percent degradants by three techniques is shown in Table 11 (2-53). The primary breakdown products that have been identified by accelerated stability testing appear to result from a [redacted] (3-89).

Stability samples from the full scale production lots have been put on test; at the time of submission, six month data on storage at below [redacted] C has been provided; this information will be updated during the review process.

10.2 Reviewer Comments - Drug Substance Stability - Container/Closure System

Storage of drug substance at below [redacted] C. appears appropriate for 6 months and more stability data will be supplied for longer periods as they become available. ***More details of extractables from the [redacted] containers are needed.***

11. Drug Product

11.1 Composition; Specifications & Methods for Ingredients; Manufacturer

[redacted]

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2 pages

11.4 *Reviewer Comments - Drug Product*

IPCs and specifications for appearance, pH, bioburden and weight of filling appear appropriate (3-453 ff). Limits of standing times, low stirring and low pressures during filtration to minimize shearing and integrity tests of the filtration also appear appropriate. The general safety test is no longer required for specified products.

12. Drug Product Stability - Container/Closure System

12.1 Overview

The container/closure system for the 20 mg/vial strength of Simulect Lyophilisate for Injection consists of a 6 mL glass vial [redacted] with a [redacted] The proposed storage temperature for the drug product is 2-8 degrees. C., i.e., USP Refrigerated storage conditions. An expiration dating of [redacted] is proposed. [redacted]

The commercial formulation of the drug product is the same as that used for the Phase III batches produced at pilot scale; thus the data available represents the product to be marketed. Results for a pilot batch [redacted] stored for 24 months show that at [redacted] storage) the lyophilized product is stable and within specifications. Data for two production scale batches at the six (6) month time point is provided in the submission and will be updated during the review period. Drug product batches on stability are given below in Table 13. The testing protocol includes [redacted]

12.2 Table 13 - Stability of Drug Product Batches

Drug Product Batches on Stability at [redacted] (market container/closure system)

Drug product batch	*Drug substance batch*	*Longest duration*
[redacted]		

4 lines

Batch ——— and the drug substance batch —— were produced at pilot scale. Drug substance batch —— was produced using ——— in the inoculum, and this batch and the drug product batch ——— is limited to technical use only (e.g., stability). Drug substance batches ——— were from the drug substance process validation studies. Similarly, drug product batches ——— are from drug product validation studies.

Quality characteristics and specifications for the ongoing stability testing program of the lyophilized drug product at ——— degrees C, and the light testing, for ———, ——— appear appropriate (3-834 ff). Stability of the reconstituted solution was performed with vials stored ——— and appeared to be stable for ——— —— degrees C. (3-881).

Adsorption studies assessing binding to the infusion set demonstrated that —— of the drug was recovered from — different sets tested (3-886).

12.3 Leachables

Leachables from all portions of the filling system and stoppers are ——— . by the standard validation assay (3-396) and are ——— acceptance limits) in the filters and stoppers by the additional —— assay. ——— ———. Leachable phthalate levels from the tubing, filter and stoppers are ——

The —— stopper washing machine demonstrates sterile washed rubber stoppers (3-715 ff).

12.4 *Reviewer Comments - Drug Product Stability - Container/Closure System*

All physical characteristics and biological activity of the commercial lots have been maintained for up to ——— *The pilot lot testing, which has the same formulation/composition as the commercial lots, has defined stability for —— at ——— C. Based upon the data presented, the proposed shelf life ———. at 2-8 degrees C. seems appropriate. Leachables and plans for the container/closure system appear within acceptable limits.*

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3 pages

14. Batch utilization overview

14.1 Batch Overview

Batch	*Drug product*	*Formulation*	*Tox*	*pK studies*	*Clinical studies*

Table

15. Environmental Assessment

Excluded under 21 CFR Part 25.31 (c).

16. Initial Summary CMC Comments/Recommendations/Sponsor Questions

16.1 Reviewer Comments

The data submitted in this BLA application support the conclusion that the manufacture of SIMULECT (basiliximab) is well controlled and leads to a product that is pure and potent. The product appears to be free from endogenous and exogenous adventitious agents in a way that meets or exceeds parameters established by the Agency. Manufacturing conditions have been validated by the use of adequate standardized methods and show that a consistent product is obtained in different production runs, maintaining the biochemical and biophysical properties of the product. The mAb produced for the clinical trials by the pilot process, and that to be licensed - which was produced by a [redacted] - appear comparable by a variety of physico-chemical and functional assays and should lead to comparable clinical safety and efficacy. However, several important issues still need to be addressed by the manufacturer and are listed below. If they can be addressed adequately, I recommend approval of this product for human use under the conditions specified in the SIMULECT package insert.

16.2 Recommendations / Questions - Issues to be addressed by the sponsor:

16.2.1. Several potential bioburden problems have occurred in the manufacture of SIMULECT in the [redacted] To confirm that these problems in manufacturing have been adequately addressed by the changes implemented, please provide detailed sterility and bioburden data on the more recently manufactured lots.

16.2.2. Please supply all specifications and certificate of analysis sheets on all human and animal products used in the establishment of cell banks and manufacture of SIMULECT. Please include information from all suppliers of human and animal materials that address possible TSE risks.

16.2.3. Please provide further details on the stability testing program regarding the statement that the by-products and degradation products defined by [redacted] chromatography were overestimated because of '[redacted] and '[redacted]" (per the Table on page 3-874 of the BLA submission).

16.2.4. Please detail the extractables and leachables that meet USP requirements from the [redacted] containers mentioned on page 3-442.

16.2.5. Please submit data demonstrating that the LAL pyrogen assay has been validated against the rabbit pyrogen assay per CFR 610.9 and 610.13.

16.2.6. Sequencing of both expression vectors showed that all exons of the chimeric antibody were intact but minor single base differences were found in non-coding regions (3-250). Please supply details of all of these differences.

16.2.7. Please supply data on the affinity of basiliximab to the IL2R regarding the batches being compared (the reference standard and ————————.), as well as the full comparability data from the ~ lot (97913) made by the final commercial process as they becomes available.

16.2.8. Because packaging of SIMULECT will now occur in a ———— facility, please describe this facility, methods of shipping drug from ———————— and validation data regarding stability of the final drug product during such shipment.

16.2.9. Please be advised that a general safety test is no longer a required assay for SIMULECT and other specified products.

16.2.10. We suggest that you perform column performance studies using model columns at scale to define acceptable limits of the performance of all columns used in the downstream processing of SIMULECT.

16.2.11. We recommend that you establish a MCB and WCB for the ————————

16.2.12. We recommend that you define the epitope on the IL2R targeted by basiliximab as described in the 1997 Points to Consider in the Manufacturing and Testing of Monoclonal Antibody Products for Human Use guidance document.

16.2.13. Your current reference standard appears appropriate, however, we suggest that you define standard operating procedures for qualifying new reference standards.

17. Addendum to the Initial Product Review

After inspection of the Basel facility, further review of the BLA, and review of responses to the above information, were received as BLA supplements dated March 25, April 7, April 9, April 17, April 22, May 1, and May 6, 1998, this addendum to the product review was added.

17.1 Responses to the above BLA product information requests

17.1.1. Regarding the potential bioburden problems that have occurred in the manufacture of SIMULECT in the new facility, the sponsor has agreed to manufacturing changes and monitoring detailed in the amendments of April 17 and These should minimize future bioburden problems in the production of SIMULECT.

17.1.2. All specifications and certificate of analysis sheets on all human and animal products used in the establishment of cell banks and manufacture of SIMULECT, as well as communications with all suppliers, have been supplied. Ongoing evaluations and follow up of donors of these products should minimize future possible TSE risks.

17.1.3. Details on the stability testing program regarding the statement that the by-products and degradation products defined by chromatography were overestimated because of " and " (per the Table on page 3-874 of the BLA submission) have been provided and do not suggest any problems with the stability data.

17.1.4. The extractables and leachables that meet USP requirements from the containers mentioned on page 3-442 have been adequately detailed and are acceptable.

17.1.5. Data has been submitted demonstrating that the LAL pyrogen assay has been validated against the rabbit pyrogen assay per CFR 610.9 and 610.13.

17.1.6. Details of the sequences of both expression vectors showed that the minor single base differences in the non-coding regions ( ) were the result of differences between the theoretical and real sequencing data and are thus inconsequential.

17.1.7. Data have been supplied on the affinity of basiliximab to the IL2R regarding the batches being compared (the reference standard and , as well as the full comparability data from the lot (. All these data suggest that the material produced by the final commercial process is comparable to that produced in the pilot plant.

17.1.8. The shipping validation protocol re shipping drug from and to the final users is adequate. It includes extensive experience in such shipments in the past and the commitment to monitor the first batches of shipped product to assure that maximum temperatures will not be exceeded.

17.1.9. The sponsor acknowledges that a general safety test is no longer a required assay for SIMULECT and other specified products for the U.S. but may continue to perform these tests since they are still required by other regulatory agencies.
17.1.10. Column performance studies using model columns at scale will be performed to define column lifetimes. Until column lifetimes are defined for the acceptable limits of the performance of all columns used in the ——— processing of SIMULECT, careful monitoring of column performance will be performed.
17.1.11. A MCB for the ——— that constitutively expresses IL-2R and is used for the receptor binding assay has been established.
17.1.12. The sponsor has presented data from phage display studies suggesting that the epitope on the IL2R targeted by basiliximab lies within residues ——
17.1.13. New standard operating procedures for qualifying new reference standards have been adopted that are acceptable.

In summary the sponsor has adequately addressed all the above issues by clarifications, submission of additional information, or by commitments for future action.

17.2 Additional CMC issues

After the Basel inspection and additional review of the BLA submission, a number of new CMC and follow-up BLA issues arose. These issues, detailed below, were transmitted to the sponsor who responded adequately to them in the May 1, 1998 supplement.

17.2.1 Regarding the purification column resin reuse:

(a) There is no periodic monitoring following the cleaning operation for the ——— columns demonstrating that the resins are consistently cleaned (no carryover) throughout the lifespan of the column. For example, after —— purification runs on the ——— column, an unidentified substance accumulated on the — resin which interferes with the packing (causing channeling and an abnormal elution) during the compression step of the operation. To remove this substance, an additional cleaning step using ——— has been implemented after every — runs. Cleaning validation studies were not performed demonstrating that ——— effectively removed this substance.

(b) There is no periodic monitoring of the process impurities (— ——— during the purification of Simulect prior to establishment of the lifespan of the column resins.

(c) Bacteriostatic effectiveness has not been demonstrated for the solutions used to store the column resins.

Please submit your proposed plan for column reuse including cleaning validation, monitoring for contaminate levels, and sanitization effectiveness for review.

The sponsor has responded adequately to this question. The sponsor has agreed to perform routine column cleaning monitoring, has defined provisional limits on process impurities, and has submitted an acceptable proposed plan for cleaning validation.

17.2.2 Not all hold periods for in-process bulk product and process buffers have been validated or the hold period cannot be supported by the validation study. For example: in-process bulk intermediates may be stored for ——— with an associated bioburden and the product characteristics have not been evaluated; ——— may be held for —— at ———— , however, ——— has been shown to promote growth (ca. two logs) of microorganisms after 3 days. These in-process bulks and buffers are not routinely or periodically monitored for bioburden. Please submit your proposed plan for holding in-process bulk intermediates and buffers that was discussed during the inspection.

The sponsor responded adequately by defining the provisional hold period limits for all buffers above and plans to perform appropriate bioburden monitoring.

17.2.3 Please submit the shipping validation protocol and data summarizing the results of the shipping validation study of the drug product from ——— ———— to retailers of Simulect.

The sponsor provided detailed information that included a shipping validation protocol and a shipping container validation report suggesting that under the conditions of shipment that SIMULECT would be stable. The sponsor has also agreed to monitor the temperature of initial shipments to assure that excessive temperatures are not encountered during the shipment of SIMULECT.

17.2.4 We recommend that maximum limits be defined for the presence of ——— ——— in the final product cation exchange column —— profiles.

The sponsor has defined a maximum action limit of ———— ——— in the final product and has agreed to define the nature of these product related peaks in the future.

17.2.5 During the inspection we noted that stability information did not reflect the current labeling in the BLA. Please submit the revised labeling describing the storage temperatures following reconstitution of Simulect.

The labeling has been modified appropriately.

17.2.6 Please assay the MCB for [redacted]

The sponsor committed to assess the MCB for [redacted]

18. Final Product Reviewer Recommendation re BLA 97-1251

After a complete and thorough review of BLA 97-1251 -- based upon the pre-BLA filing materials, a 93 volume paper BLA and electronic (eBLA) submission, and evaluation of additional information submitted by the sponsor as supplements dated March 25, April 7, April 9, April 17, May 1, and May 6, 1998 -- I recommend approval of this product for human use under the conditions specified in the SIMULECT package insert.